REMARKS

I. Status of Claims

Claims 23-47 were pending in this application at the time of the Final Office Action (referred to hereinafter as FOA). Claims 1-22 were previously cancelled. Claims 37 and 44-47 have been amended. Support for amendments to claim 37 can be found throughout the specification, as originally filed, for example, at least at [0014], [0017], [0021]-[0025], [0053] and [0073]. Amendments to claims 44-47 corrects typographical errors relating to claim dependency and add no new matter. Accordingly, no new matter has been added by any claim amendments.

Entry of claims is respectfully requested since the claims as amended place the case in condition for allowance.

The Applicant does not acquiesce to the propriety of any rejections and the present amendments should not be construed as an abandonment or disclaimer of any originally-disclosed subject matter, and the Applicant reserves the right to file continuing or related applications directed to all disclosed subject matter.

II. Rejection Under 35 U.S.C. §112 , 2nd Paragraph Rejection

Claim 37 stands rejected under 35 U.S.C. §112, 2nd paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 37, as presently amended, overcomes the 35 U.S.C. §112, 2nd paragraph rejections. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 44-47 stand rejected under 35 U.S.C. §112, 2nd paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 44-47 have been amended to correct their dependency from claim 1, which is cancelled, to claim 38. Accordingly, claims 44-47, as presently amended, overcome the 35 U.S.C. §112 , 2nd paragraph rejections. Reconsideration and withdrawal of the rejection are respectfully requested.

III. 35 U.S.C. 103(a) Rejection

A. Claims 23-36, 38, 39 and 44-46 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 5,962,641 to Nelson et al. ("Nelson") in view of Chaga et al. (J. Chromatogr. A 864 (2), 1999, pages 247-256) ("Chaga"); and U.S. Patent No. 6,441,146 to Minh ("Minh"); and further in view of U.S. Patent No. 4,654,267 to Ugelstad et al. ("Ugelstad").

Applicant respectfully traverses. According to the M.P.E.P. § 2143.03, a threshold requirement for establishing a *prima facie* case of obviousness is that all elements of the claim or claims rejected must be found in the combination of references cited, and there must be a clear reasoning as to why such a combination would produce the results of the presently claimed embodiments. In addition, when "an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious."

Furthermore, in accordance to Federal Circuit jurisprudence, the mere assertion of obviousness does not establish a *prima facie* case of obviousness. In deriving this inference, the FOA is evidently proceeding with an impermissible "hindsight analysis" of the invention. This is clearly improper under the law. To imbue one of ordinary skill in the art with knowledge of the instant invention, where no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 312-313 (Fed. Cir. 1983).

In the present case, Applicant submits that the combination of references cited by the Examiner fail to teach each and every element of the rejected claims and further lack any reasoning as to why such references may be combiner and/or if combined would lead the skilled artisan to the claimed invention.

For example, Nelson fails to teach or suggest at least the following elements of independent claim 23 (upon which claims 24-36 are dependent); including: "contacting the tagged protein with a conjugate of a chelating agent and the polymer particle to form a protein-polymer particle-chelating agent metal ion complex, **wherein the chelating**

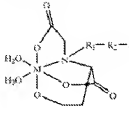
agent is covalently linked to the polymer particle;" and; "**contacting the complex with a carbodiimide to form a covalently bound protein**;" "wherein: the **tag comprises at least two histidine residues; the tag comprises at least two lysine residues**." (**emphasis added**)

Nelson further fails to teach or suggest at least the following elements of independent claim 38 (and its dependent claims 39-47) including: "A **protein covalently bound** to a magnetic polymer particle, wherein: the protein comprises a tag sequence;" "**the tag sequence comprises at least two histidine residues and at least two lysine residues**;" "the magnetic polymer particle comprises a linking group; and the **linking group is covalently bound to at least one of the at least two lysine residues** via amide linkages, wherein the linking group comprises at least three linking atoms." (**emphasis added**)

For example, as acknowledged by the FOA on page 7, Nelson does not teach "a tag comprising at least two histidine residues and at least two lysine residues." Neither is there a suggestion for using such a tag. Furthermore, Applicants have found no teaching or suggestion in Nelson for forming "covalent linkages" with the "protein/tag" as recited in the present claims either. In addition, Applicants have found no teaching or suggestions for the use of carbodiimide's including dicyclohexylcarbodlimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC), in Nelson as described in claim 23 and its dependents (this is also acknowledged by the FOA on at least page 8).

Nelson appears to teach no more than the following as recited in column 2, lines 12-51, copied below for the convenience of the Examiner:

tion method which employs immobilized carboxymethylated aspartate (CM-Asp) ligands specifically designed for purification of recombinant proteins fused with polyhistidine tags. The new purification method is based upon the CM-Asp chelating matrix having the following structure:



A general description of the matrix used in the invention and illustrated above is.

M=transition metal ion in a 2^+ oxidation state with a coordination number of 6;

R_1=a linking arm connecting the nitrogen atom of CM-Asp with R_2;

R_2=a functional linking group through which CM-Asp linking arm R_2 is connected to R_3;

R_3=a polymer matrix, e.g., those polymer matrices typically used in affinity or gel chromatography.

In a preferred embodiment·

M=Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+};

R_1=—$CH_2CH(OH)CH_2$— or —$CH_2(OH)CH_n$—O—$CH_2CH(OH)CH_2$—;

R_2=O, S, or NH; and

R_3=agarose.

In a particularly preferred embodiment.

M=Co^{2+};

R_1=$CH_2CH(OH)CH_2$;

R_2=O; and

R_3=agarose, cross-linked.

Chaga fails to teach or suggest all the missing deficiencies either. For example, Applicant has failed to find any teaching or suggestion in Chaga for at least the following elements of independent claim 23 (upon which claims 24-36 are dependent); including: "**contacting the tagged protein with a conjugate of a chelating agent and the polymer particle to form a protein-polymer particle-chelating agent metal ion complex**," "wherein **the chelating agent is covalently linked to the polymer particle**;" and; "**contacting the complex with a carbodiimide to form a covalently bound protein**." (**emphasis added**).

Chaga further fails to teach or suggest at least the following elements of independent claim 38 and its dependents claims 39-47 including: "A **protein covalently**

bound to a magnetic polymer particle, wherein: the protein comprises a tag sequence;" "the magnetic polymer particle comprises a linking group; and the **linking group is covalently bound to at least one of the at least two lysine residues** via amide linkages, wherein the linking group comprises at least three linking atoms." (**emphasis added**)

For example, as acknowledged by the FOA on page 8, neither Nelson nor Chaga teach "contacting a protein-polymer particle-chelating agent metal ion complex with a carbodiimide to form a covalently bound protein." Neither is there a suggestion for such contacting step. Furthermore, Applicant has found no teaching or suggestion in Chaga for methods or compositions of forming/having "covalent linkages" with the "protein/tag" as recited in the present method and compositions claims respectively. In addition, Applicant has found no teaching or suggestions for the use of carbodiimide's including dicyclohexylcarbodlimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC), in Chaga as described in claim 23 and its dependents (this is also acknowledged by the FOA on at least page 8).

At best Chaga appears to describe "cloning a natural HAT tag at the N-terminus of three recombinant proteins" and "expression, extraction and purification of said proteins in one chromatographic step" (See abstract of Chaga). Absent the teachings or suggestion of at least the above recited elements of independent claims 23 and 38 (and their dependents), Nelson, alone or in combination, with Chaga, do not lead the skilled artisan to the claimed methods and compositions of the instant claims.

Minh also fails to teach or suggest these missing elements and also fails to provide any motivation to combine these elements. For example, Minh fails to teach or suggest at least the following elements of independent claim 23 (upon which claims 24-36 are dependent; including: "contacting the tagged protein **with a conjugate of a chelating agent and the polymer particle to form a protein-polymer particle-chelating agent metal ion complex, wherein the chelating agent is covalently linked to the polymer particle**;" and; "**contacting the complex with a carbodiimide to form a covalently bound protein**;" "wherein: the **tag comprises at least two histidine residues; the tag comprises at least two lysine residues**." (**emphasis added**).

Minh further fails to teach or suggest at least the following elements of independent claim 38 and its dependent claims 39-47 including: "A **protein covalently**

bound to a magnetic polymer particle, wherein: the protein comprises a tag sequence;" "**the tag sequence comprises at least two histidine residues and at least two lysine residues**;" "**the magnetic polymer particle comprises a linking group**; and the **linking group is covalently bound to at least one of the at least two lysine residues** via amide linkages, wherein the linking group comprises at least three linking atoms." (**emphasis added**)

For example, Minh appears to teach no more than "manufacture methods of PDC resins" (which, as are known to the skilled artisan, are non-magnetic polymer particles) that may interact with "histidine/cystine residues" (see column 2, lines 11-21). Additional differences over Minh are already described in the present specification, portions of which are reproduced below for convenience of the Examiner in at least [0009]-[0012], which recite:

> [0009] In U.S. Pat. No. 6,441,146 (Minh) a method for the covalent immobilisation of a protein is described involving contacting the protein with a non-magnetic resin bound to a pentadentate chelator coordinating copper (II) ions. The resulting complex is contacted with carbodiimide and the copper (II) ions removed to allow formation of the immobilised protein.
>
> [0010] The protein suggested for use in this method is a bovine serum albumin and a suitable resin is Sepharose. It has been found however, that copper (II) ions, are not ideal metal ions for this process since these chelate the pentadentate ligand strongly and the strength of this interaction causes much non-specific binding during the covalent immobilisation step, i.e. carbodiimide treatment.
>
> [0011] The method in Minh allows binding to occur between the chelating ligand and any naturally occurring lysine residues in the bovine serum albumin (BSA). The BSA in Minh may therefore have many orientations of bound ligand making the technique unsuitable for purification or amplification.
>
> [0012] It has now been found that a chelating ligand, e.g. Cm-Asp chelating ligand, can be covalently bound to a polymer particle giving rise to a moiety that possesses the ability to bind covalently to tags on recombinant proteins thereby allowing the skilled biochemist more flexibility in his assaying procedures. Moreover, the chelating ligand should preferably coordinate a metal ion such as cobalt (II) ions to minimise non-specific binding during immobilisation.

(present specification [0009]-[0012])

The skilled artisan, upon review of Minh, would agree that several elements of the present claims are missing in Minh that are also not taught or suggested by Nelson and/or Chaga. Furthermore, "non-specific binding due to use of carbodiimide treatment in Minh" (see [0010]) in fact appears to "teach away" from using "carbodiimide" in the current claims.

Furthermore, as acknowledged by the FOA neither Nelson, Chaga or Minh teach that the chelating ligand is attached to a magnetic polymer particle. Absent the teachings or suggestion of at least the above recited elements of independent claims 23, 37 and 38 (and their dependents) in Nelson, Chaga and/or Minh, these references, alone or in combination, do not lead the skilled artisan to the claimed methods and compositions of the instant patent application.

Ugelstad while teaching magnetic polymer particles fails to teach at least the following elements of independent claim 27, which are also not taught by Nelson, Chaga and/or Minh including: "**contacting the tagged protein with a conjugate of a chelating agent and the polymer particle to form a protein-polymer particle-chelating agent metal ion complex, wherein the chelating agent is covalently linked to the polymer particle**;" and; "**contacting the complex with a carbodiimide to form a covalently bound protein**;" "wherein: the **tag comprises at least two histidine residues; the tag comprises at least two lysine residues**." (**emphasis added**).

Ugelstad further fails to teach or suggest at least the following elements of independent claim 38 and its dependents claims 39-47, which are also not taught by Nelson, Chaga and/or Minh, including: "A **protein covalently bound** to a magnetic polymer particle, wherein: the protein comprises a tag sequence;" "**the tag sequence comprises at least two histidine residues and at least two lysine residues**;" "the magnetic polymer particle comprises a linking group; and the **linking group is covalently bound to at least one of the at least two lysine residues** via amide linkages, wherein the linking group comprises at least three linking atoms."

Furthermore, additional differences and several disadvantages for using one or more of the references cited herein is outlined in the present specification at least at [0004] – [0011]. In addition, the surprising properties of the methods and the compositions of the instant patent application as claimed are not found in the cited art.

The combination of cited references fails to teach or suggest at least the above listed limitations of independent claims 23 and 38 (and their dependent claims at least for analogous reasons). Since the combination of references does not teach each and every limitation of claims 23 and 38, a *prima facie* case of obviousness has not been established with respect to these claims or the claims depending from claims 23 or 38 (and their dependents). To combine the references in a manner combined by the FOA is at best a "hindsight analysis" attempt to arrive at the claimed invention. One of skill in the art would, according to the analysis of the FOA, have to substitute so many factors that are not taught or suggested in each reference and also not taught or suggested in combinations of references, to allegedly arrive at the claimed invention.

However, even this analysis, which is clearly improper under the present law, is still insufficient to arrive at the claimed embodiments, absent the teachings of the present specification, as shown in the evidence above. For example, Minh "teaches away" from using "carbodiimide." To imbue one of ordinary skill in the art with knowledge of the instant invention, where no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 312-313 (Fed. Cir. 1983).

In view of the evidence above, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) to claims 23-36, 38, 39 and 44-46.

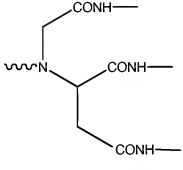
B. Claims 37, 40-43 and 47 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 5,962,641 to Nelson et al. ("Nelson") in view of Chaga et al. (J. Chromatogr. A 864 (2), 1999, pages 247-256) ("Chaga"); and U.S. Patent No. 6,441,146 to Minh ("Minh"); and further in view of U.S. Patent No. 4,654,267 to Ugelstad et al. ("Ugelstad") and further in view of U.S. Patent No. 6,242,581 to Nelson et al. ("'581 patent").

Applicant respectfully traverses. Differences from Nelson, Chaga, Minh and Ugelsatd over independent method claim 23 (and its dependents) and compositions

recited in independent claim 38 and its dependents (39-47) are already described in sections above.

For the rejection of claims 40-43 and 47, which depend on claim 38, the reasons and evidence set forth above apply and hence these claims are not obvious over Nelson, Chaga, Minh and Ugelsatd, alone or in combination, at least for analogous reasons. The '581 patent also fails to teach or suggest the missing limitations of claim 38 that are not taught by Nelson, Chaga, Minh and Ugelstad. For example, the '581 patent also fail to teach at least the following elements of claim 38, including: "A **protein covalently bound to a magnetic polymer particle**, wherein: the protein comprises a tag sequence; **the tag sequence comprises at least two histidine residues and at least two lysine residues**; the magnetic polymer particle comprises a linking group; and **the linking group is covalently bound to at least one of the at least two lysine residues via amide linkages**, wherein the linking group comprises at least three linking atoms." (**emphasis added**) Since claims 40-43 and 47 are dependent on claim 38, they incorporate by reference at least these limitations and at least for analogous reasons as set forth in sections above are not obvious the '581 patent when combined with Nelson, Chaga, Minh and Ugelstad.

With regard to the rejection of claim 37, Nelson fails to teach or suggest at least the following elements of currently amended independent claim 37 including: "Polymer particle - linker - protein; wherein: the linker comprises the structure:



and;

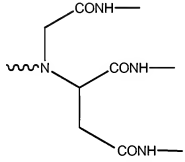
the protein comprises a tag sequence comprising at least two histidine residues and at least two lysine residues, wherein the linker further comprises a structure:

-NH-L_1-Er-Nr-L_2-

wherein L_1 is a linker comprising 1 to 10 atoms, L_2 is a linker comprising 1 to 10 atoms, E_r is an electrophile residue, and N_r is a nucleophile residue;" and "wherein **the linker is covalently bound to at least one of the at least two lysine residues of the tag sequence** of the protein via amide linkages."

For example, as acknowledged by the FOA on page 7, Nelson does not teach "a tag comprising at least two histidine residues and at least two lysine residues." Neither is there a suggestion in nelson for using such a tag. Furthermore, Applicants have found no teaching or suggestion in Nelson for "linker" "covalently bound" to the "protein/tag" as recited in the present claim 37 either.

Chaga also fails to teach or suggest at least the following elements of independent claim 37 including: "Polymer particle - linker - protein; wherein: the linker comprises the structure:



and;

the protein comprises a tag sequence comprising at least two histidine residues and at least two lysine residues, **wherein the linker further comprises a structure:**

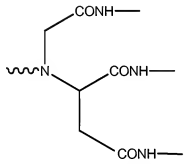
-NH-L_1-Er-Nr-L_2-

wherein L_1 is a linker comprising 1 to 10 atoms, L_2 is a linker comprising 1 to 10 atoms, E_r is an electrophile residue, and N_r is a nucleophile residue;" and **"wherein the linker is covalently bound to at least one of the at least two lysine residues of the tag sequence** of the protein via amide linkages."

For example, as acknowledged by the FOA on page 8, neither Nelson nor Chaga teach "contacting a protein-polymer particle-chelating agent metal ion complex with a

carbodiimide to form a covalently bound protein." Neither is there a suggestion for such contacting step. Furthermore, Applicant has found no teaching or suggestion in Chaga for compositions of "wherein the linker is covalently bound" to the "protein/tag" as recited in the present composition claim 37. In addition, Applicants have found no teaching or suggestions for the use of carbodiimide's in Chaga as described in claim 23 and its dependents to arrive at the claimed compositions of claim 37 (acknowledged by the FOA on at least page 8).

Minh also fails to teach or suggest at least the following elements of independent claim 37 including: "Polymer particle - linker - protein; wherein: the linker comprises the structure:



and;

the protein comprises a tag sequence comprising at least two histidine residues and at least two lysine residues, wherein the linker further comprises a structure:

-NH-L_1-Er-Nr-L_2-

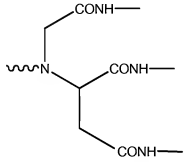
wherein L_1 is a linker comprising 1 to 10 atoms, L_2 is a linker comprising 1 to 10 atoms, E_r is an electrophile residue, and N_r is a nucleophile residue;" and

"wherein the linker is covalently bound to at least one of the at least two lysine residues of the tag sequence of the protein via amide linkages."

The skilled artisan, upon review of Minh, would agree that several elements of the present claims are missing in Minh that are also not taught by Nelson and/or Chaga. Furthermore, as acknowledged by the FOA neither Nelson, Chaga or Minh teach that the chelating ligand is attached to a magnetic polymer particle. Absent the teachings or suggestion of at least the above recited elements of independent claim 37 in Nelson,

Chaga and/or Minh, these references, alone or in combination, do not lead the skilled artisan to the claimed compositions of claim 37.

Ugelstad also fails to teach or suggest at least the following elements of independent claim 37, which are also not taught by Nelson, Chaga and/or Minh, including: "**Polymer particle - linker - protein**; wherein: the linker comprises the structure:



and;

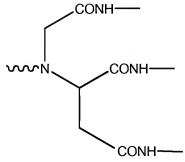
the protein comprises a tag sequence comprising at least two histidine residues and at least two lysine residues, wherein the linker further comprises a structure:

-NH-L_1-Er-Nr-L_2-

wherein L_1 is a linker comprising 1 to 10 atoms, L_2 is a linker comprising 1 to 10 atoms, E_r is an electrophile residue, and N_r is a nucleophile residue;" and

"wherein the linker is covalently bound to at least one of the at least two lysine residues of the tag sequence of the protein via amide linkages."

The '581 patent also fails to teach or suggest at least the following elements of currently amended independent claim 37 including: "Polymer particle - linker - protein; wherein: the linker comprises the structure:



and;

the protein comprises a tag sequence comprising at least two histidine residues and at least two lysine residues, wherein the linker further comprises a structure:

-NH-L_1-Er-Nr-L_2-

wherein L_1 is a linker comprising 1 to 10 atoms, L_2 is a linker comprising 1 to 10 atoms, E_r is an electrophile residue, and N_r is a nucleophile residue;" and "wherein **the linker is covalently bound to at least one of the at least two lysine residues of the tag sequence** of the protein via amide linkages."

The combination of cited references fails to teach or suggest at least the above listed limitations of independent claim 37 and claims 40-43 and 47 that are dependent on claim 38 (and their dependent claims at least for analogous reasons). Since the combination of references does not teach each and every limitation of claims 37, 40-43 and 47, a *prima facie* case of obviousness has not been established with respect to these claims. To combine the references in a manner combined by the FOA is at best a "hindsight analysis" attempt to arrive at the claimed invention. One of skill in the art would, according to the analysis of the FOA, have to substitute so many factors that are not taught or suggested in each reference and also not taught or suggested in combinations of references, to allegedly arrive at the claimed invention.

However, even this analysis, which is clearly improper under the present law, is still insufficient to arrive at the claimed embodiments, absent the teachings of the present specification, as shown in the evidence above.

In view of the evidence above, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) to claims 37, 40-43 and 47.

IV. Provisional Double-Patenting Rejection

A. Claims 23-47 were provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-17, 19-23 and 27 of copending Application No. 12/643,617 (PGPUB 2010/0222508), which is a

continuation of Application No. 10/562,694, now abandoned, in view of Chaga; and Minh, issued on 08/27/2002 (cited in the specification).

Applicant respectfully requests that the provisional non-statutory obviousness-type double patenting rejection be held in abeyance until allowance of the instant application and/or copending Application No. 12/643,617.

In addition, Applicant respectfully submits that sections above describe in detail the differences over Chaga and Minh to the present claimed invention. Consideration of the evidence and arguments set forth above is requested.

CONCLUSION

Applicant believes that all outstanding matters in this case have been addressed. In view of the above amendment to claims and remarks, it is submitted that this application and pending claims are now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (512) 721-3657.

Respectfully Submitted,

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